

FIGURE 1

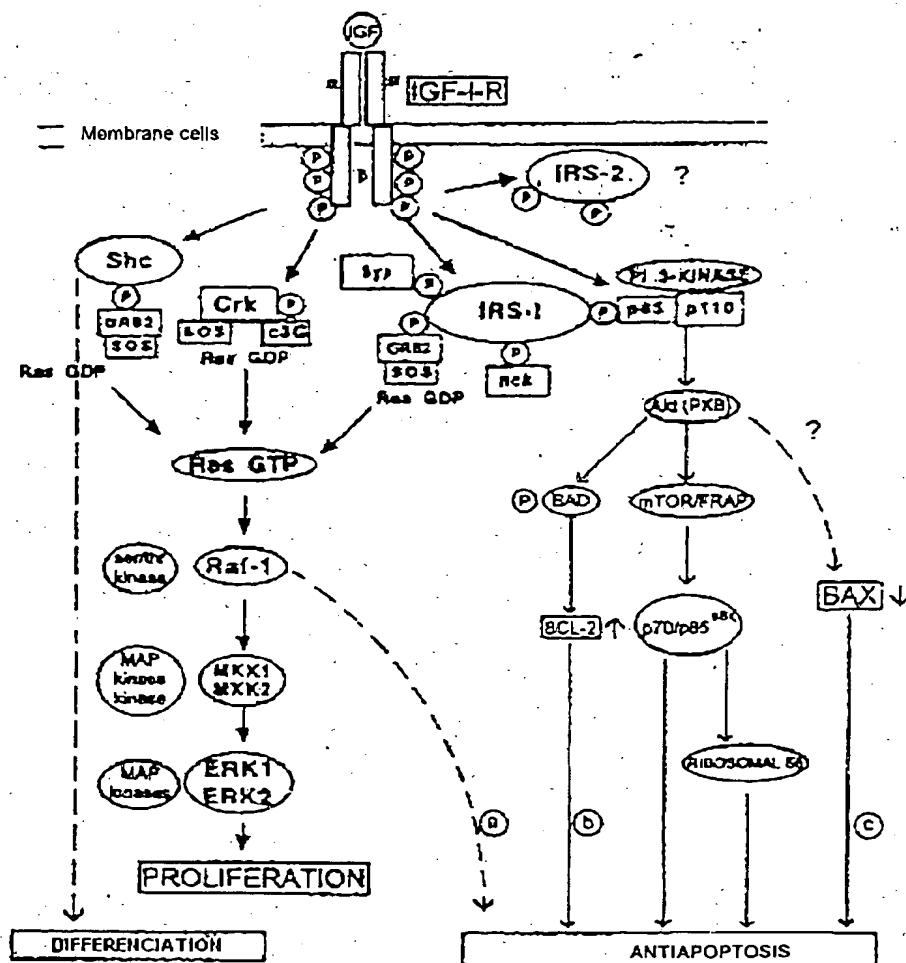


FIGURE 2

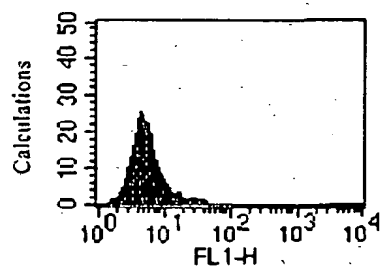


FIGURE 3A

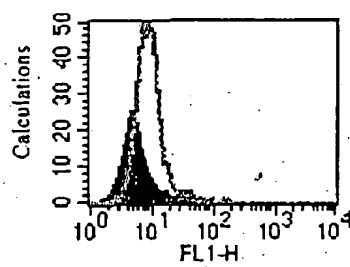


FIGURE 3B

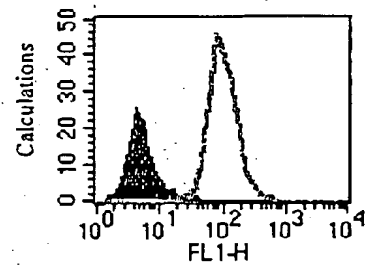
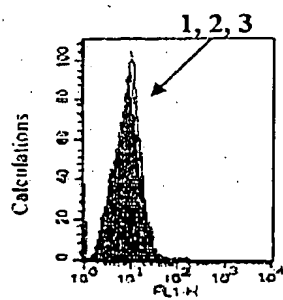
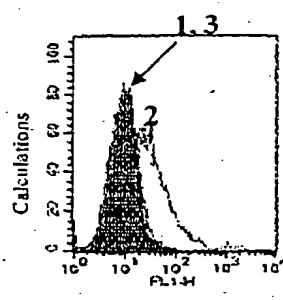


FIGURE 3C



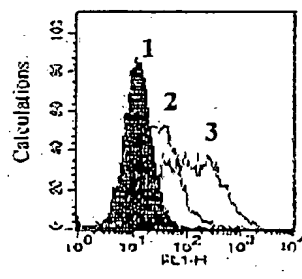
Nontransfected cells

FIGURE 4A



IGF-IR+ cells

FIGURE 4B



IR+ cells

FIGURE 4C

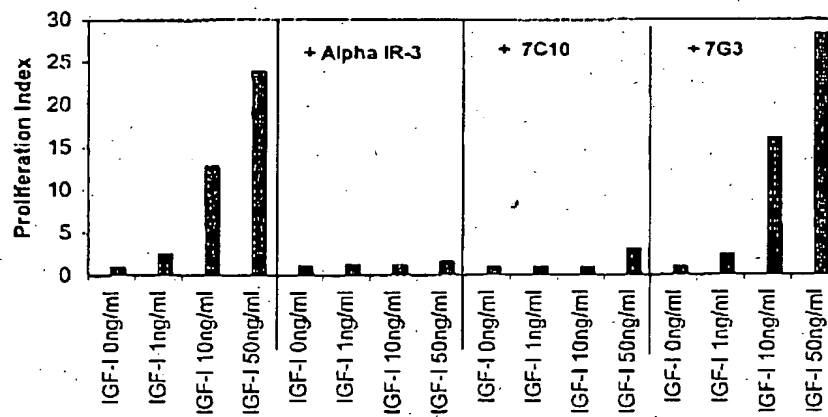


FIGURE 5

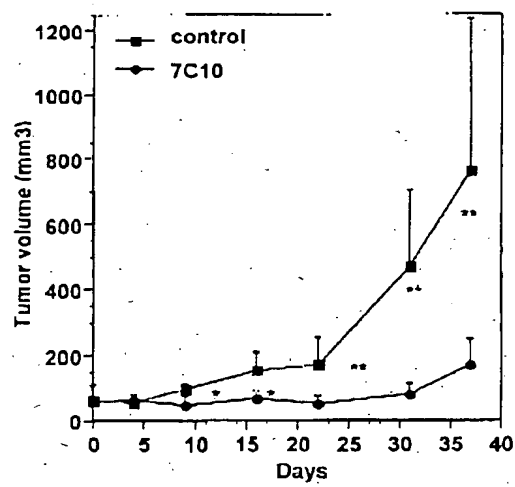


FIGURE 6A

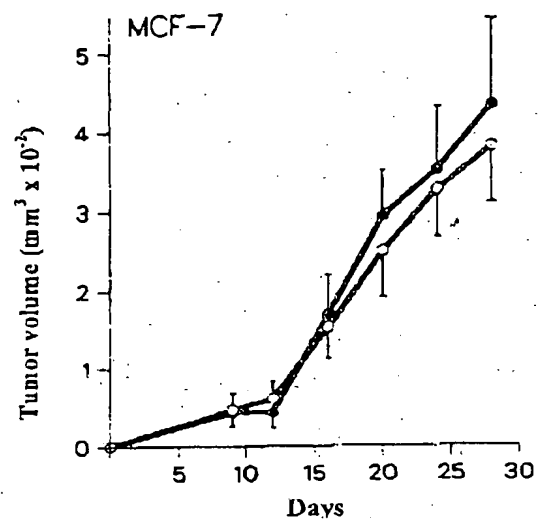


FIGURE 6B

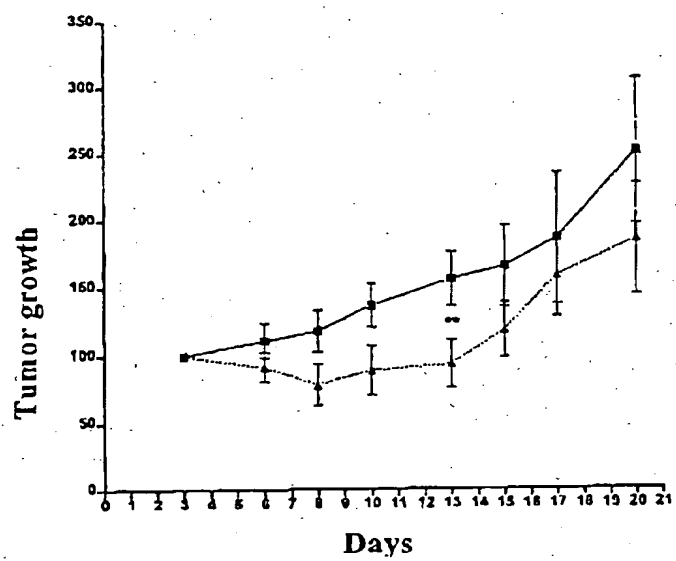


FIGURE 6C

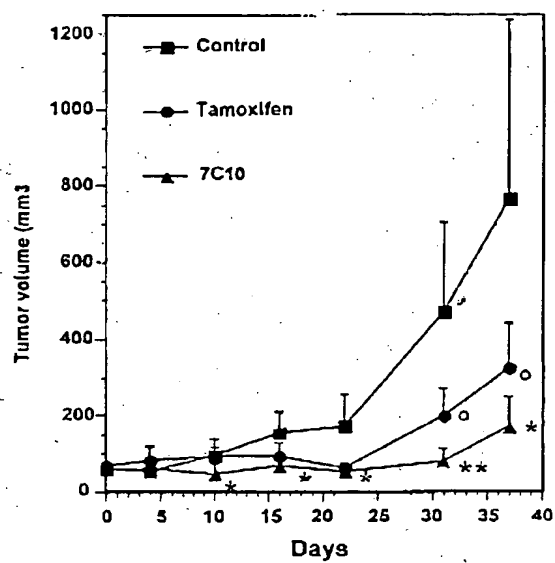


FIGURE 7

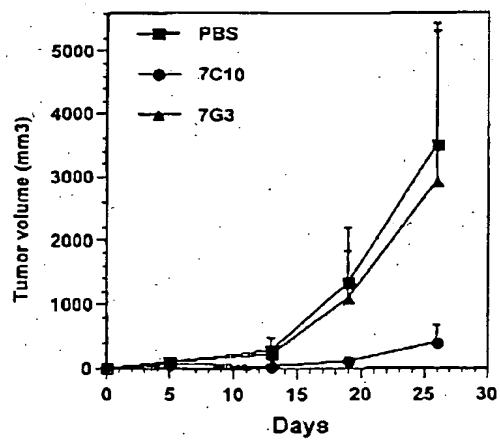


FIGURE 8A

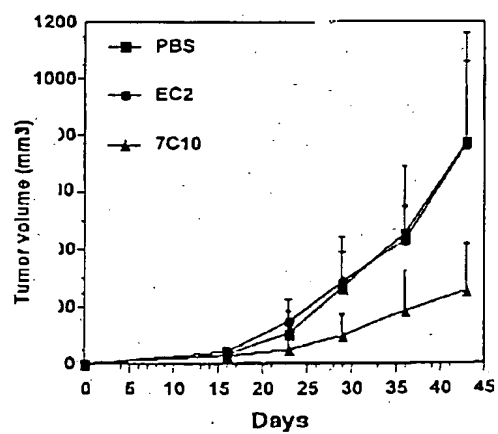


FIGURE 8B

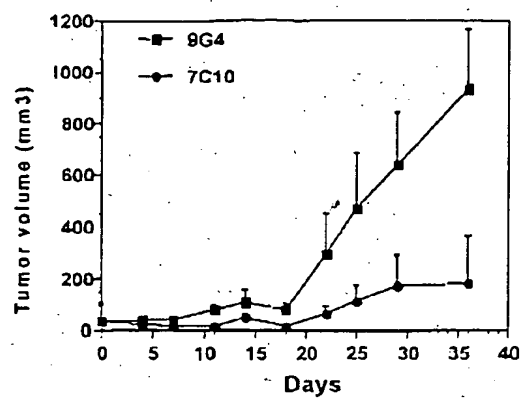


FIGURE 8C

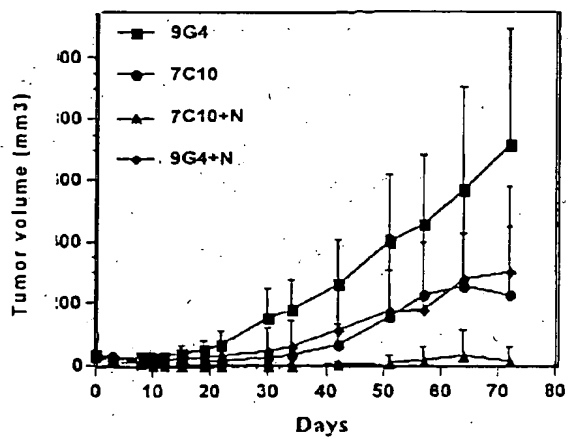


FIGURE 9

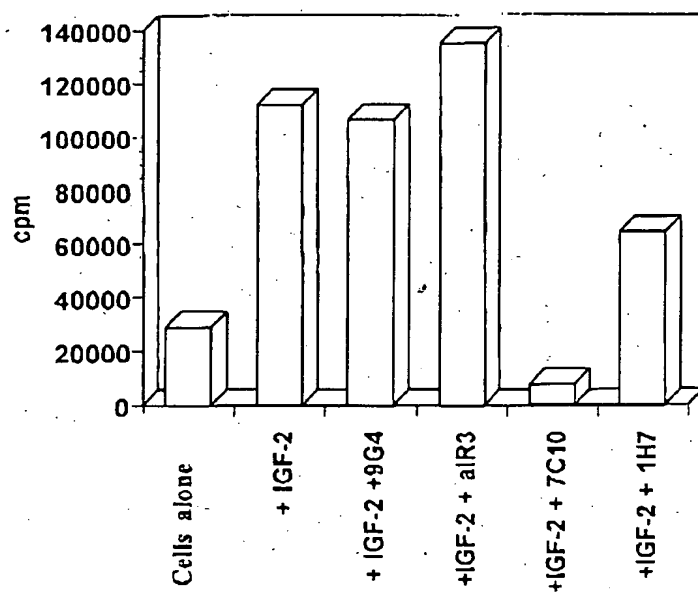


FIGURE 10

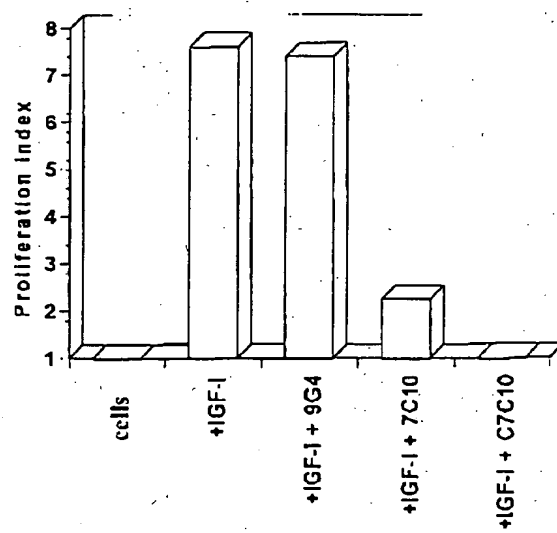


FIGURE 11

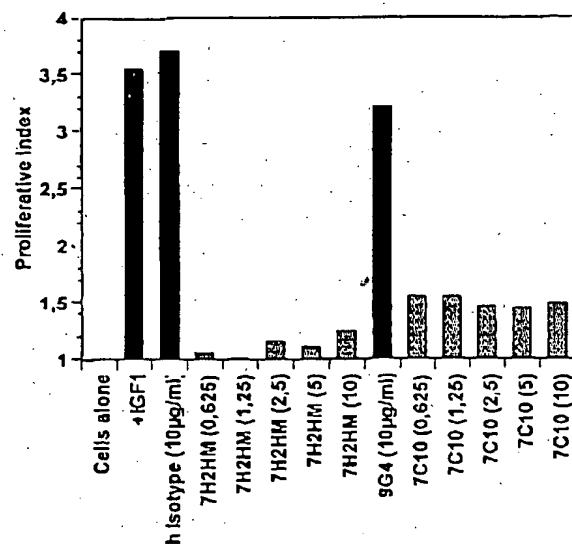


FIGURE 12

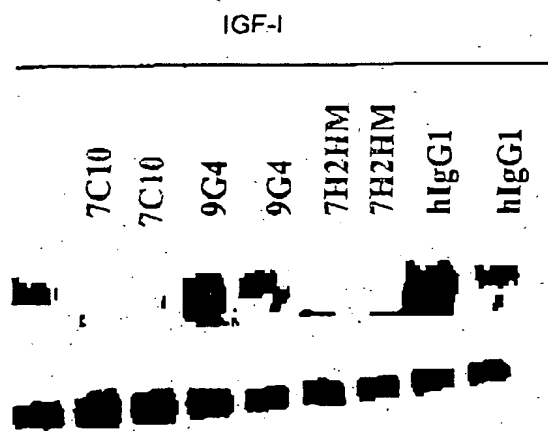


FIGURE 13

```

1 ATGAAGTTGCCTGTTAGCCTGTTGGTGCTGATGTTCTGGATTCTGCTTCCAGAAGTGAT
-----+-----+-----+-----+-----+ 60
TACTTCAACGGACAATCCGACAACCACCACTACAAGACCTAAGGACGAAGGTCTTCACTA
ATGAAGTTGCCTGTTAGGCTGTTGGTGCT
oligo MKV-1      L M F W I P A S R S D -
                  3' end      leader peptide
61 GTTTTGATGACCCAAATTCCACTCTCCCTGCCTCTCAGTCTTGGAGATCAAGCCTCCATC
-----+-----+-----+-----+-----+ 120
CAAACTACTGGGTTTAAGGTGAGAGGGACGGACAGTCAGAACCCTCTAGTTCGGAGGTAG
V L M T Q I P L S L P V S L G D O A S I -
121 TCTTCAGATCTAGTCAGAGCATTGTACATAGTAATGGAACACCTATTTACAATGGTAC
-----+-----+-----+-----+-----+ 180
AGAACGTCTAGATCACTCTCGTAACATGTATCATTACCTTTGTGGATAAATGTTACCATG
S C R S S O S I V H S N G N T Y L Q W Y -
                  CDR 1
181 CTGCAGAAACCAGGTCACTCTCCAAACCTCTGATCTACAAAGTTTCCAACCGACTTTAT
-----+-----+-----+-----+-----+ 240
GACGTCTTTGGTCCAGTCAGAGGTTTCGAGGACTAGATCTTTCAAAGGTTGGCTGAAATA
L Q K P G Q S P K L L I Y K V S N R L Y -
                  CDR 2
241 GGGGTCCCAGACAGGTTCACTGGCAGTGGATCAGGGACAGATTTCACACTCAAGATCAGC
-----+-----+-----+-----+-----+ 300
CCCCAGGGTCTGTCCAAGTCACCGTCACCTAGTCCCTGTCTAAACTGTGAGTTCAGTCG
G V P D R F S G S G S G T D F T L K I S -
301 AGCGTGGAGGCTGAGGATCTGCCAGTTTATTACTGCTTTCAAGGTTTCAATGTTCCGTGG
-----+-----+-----+-----+-----+ 360
TCGCACCTCCGACTCCTAGACCCTCAAATAATGACGAAGTTCCAAGTGTACAAGGCACC
S V E A E D L G V Y Y C F Q G S H V P W -
                  CDR 3
361 ACGTTCGGTGGAGGCACCAAGCTGGAATCAAACGGGCTGATGCTGCACCAACTGTATCC
-----+-----+-----+-----+-----+ 420
TGCAAGCCACCTCCGTGGTTCGACCTTTAGTTTGCCCGACTACGACGTGGTTGACATAGG
T F G G G T K L E I K
MKC oligo
TAGAAGGGTGGTAGGTCA
ATCTTCCCACCATCCAGT
421 -----+-----+-----+-----+ 438
TAGAAGGGTGGTAGGTCA

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FIGURE 14

1 ATGATGGTCTTAAGTCTTCTGTACCTCTTGACAGCCATTCTGGTATCCTGTCTGTATGTA 60
 TACTACCACAAATTCAGAAGACATGGACAACCTGTCGGTAAGGACCATAGGACAGACTACAT
 MHV-12 ATGATGGTGTAAAGTCTTCTGTACCT
 MHV-8 ATGAGAGTGCTGATTCTTTTGTG

L L T A I P G I L S D V -
 3' end leader peptide

61 CAGCTTCAGGAGTCAGGACCTGGCCTCGTGAAACCTTCTCAGTCTCTGTCTCTCACCTGC 120
 GTCGAAGTCCTCAGTCTCGGACCGGAGCACTTTGGAAGAGTCAGAGACAGAGAGTGGACG
 Q L Q E S G P G L V K P S O S L S L T C -
 TCTGTACCCGGCTACTCCATCACCGGTGGTTATTTATGGAACCTGGATCCGGCAGTTTCCA
 121 AGACAGTGGCCGATCACCTAGTGGCCACCAATAAATACCTTGACCTAGGCCGTCAAAGGT 180
 S V T G Y S I T G G Y L W N W I R Q F F -
 CDR 1
 CGAAACAACTGGAGTGCATGGGCTACATAAGCTACGACGGTACCAATAACTACAAACCA
 181 CCTTTGTTGACCTCACCTACCCGATGTATTCCATGCTGCCATGGTTATTCTATGTTTGGT 240
 G N K L E W M G Y I S Y D G T N N Y K P -
 CDR 2
 TCTCTCAAAGATCGAATCTCCATCACTCGTGACACATCTAAGAACCAGTTTTCTCTGAAG
 241 AGACAGTTTCTAGCTTAGAGGTACTGAGCACTGTGTAGATTCTTGGTCAAAAAGGACTTC 300
 S L K D R I S I T R D T S K N Q F F L K -
 TTCAATCTGTGACTAATGAAGACACAGCTACATATTACTGTGCAAGATACGGTAGGGTC
 301 AACTTAAGACACTGATTACTTCTGTGTGATCTATAATGACACGTTCTATCCCATCCAG 360
 I N S V T N E D T A T Y Y C A R Y G R V -
 CDR 3
 GGG
 TTCTTTGACTACTGGGGCCAAGGCACCACTCTCACAGTCTCCTCAGUCAAACGACACCC
 361 AAGAAACTGATGACCCCGGTTCCGTGGTGAGAGTETCAGAGGAGTCGGTTTTGCTGTGGG 420
 F F D Y W G Q G T T L T V S S
 oligo MHC-1
 GGTAGACAGATAGGTGAC
 CCATCTGTCTATCCACTG
 421 GGTAGACACATAGGTGAC 438

FIGURE 15

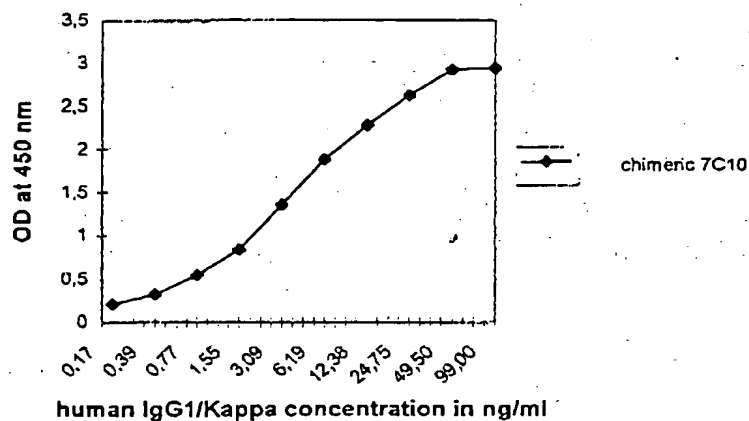


FIGURE 16

	3	7		CDR 1
7C10 VL mouse	DVL	MTQ	IPLSLPVSLGDQASISC	RSSQSIVHSNGNTYLQ
DRB1-4.3		T		E
C94-5B11'CL		T		E
Kabat sgII mouse	V	T		L E

	CDR 2
7C10 VL mouse	WYLQKPGQSPKLLIY KVSNRLY GVPDRFSGSGSGTDETL
DRB1-4.3	FS
C94-5B11'CL	FS
Kabat sgII mouse	FS

	77	CDR 3
7C10 VL mouse	KISSVEAEDLGVIYC	FQGSHPWT FGGGTKLEIK
DRB1-4.3	R	F S D
C94-5B11'CL	R	
Kabat sgII mouse	R	T Y

FIGURE 17

CDR 1

7C10 VL mouse	DVLMTQIPLSLPVSLGDQASISC	<u>RSSQSIVHSNGNTYLQ</u>
GM607	.IV...S.....TP.EP.....LL....YN..D
DPK15/A19	.IV...S.....TP.EP.....LL....YN..D
Kabat sgII hu	.IV...S.....TP.EP.....LL..D.XX..X

CDR 2

7C10 VL mouse	WYLQKPGQSPKLLIY	<u>KVSNRLY</u>	GVPDRFSGSGSGTDFTLK
GM607Q....	LG...AS
DPK15/A19Q....	LG...AS
Kabat sgII huQ....	L...AS

CDR 3

7C10 VL mouse	ISSVEAEDLGVIYC	<u>FGGSHVPWT</u>	FGGGTKLEIK
GM607	..R.....V.....	M.ALQT.Q.	..Q...V...
DPK15/A19	..R.....V.....	M.ALQT.	
Kabat sgII hu	..R.....V.....	M.ALQX.R.	..Q...V...

FIGURE 18

CDR 1

7C10 VL mouse	DVLMTQIPLSLPVSLGDQASISC	<u>RSSQSIVHSNGNTYLQ</u>
GM 607	.IV...S.....TP.EP.....LL....YN..D
7C10 VL Humanized 1	..V...S.....TP.EP.....
7C10 VL Humanized 2	.IV...S.....TP.EP.....

CDR 2

7C10 VL mouse	WYLQKPGQSPKLLIY	<u>KVSNRLY</u>	GVPDRFSGSGSGTDFTL
GM 607Q....	LG...AS
7C10 VL Humanized 1Q....		
7C10 VL Humanized 2Q....		

CDR 3

7C10 VL mouse	KISSVEAEDLGVIYC	<u>FGGSHVPWT</u>	FGGGTKLEIK
GM 607	..R.....V.....	M.ALQT.Q.	..Q...V...
7C10 VL Humanized 1	..R.....V.....		..Q...V...
7C10 VL Humanized 2	..R.....V.....		..Q...V...

FIGURE 19

MluI

1 GTCAGAACGCGTGCCGCCACCATGAAGTTCCTGTTAGGCTGTGGTGCTCATGTTCTGG 60
 -----+-----+-----+-----+-----+
 CAGTCTTGCGCACGCGGTGGTACTTCAACGGACAATCCGACAACCACGACTACAAGACC

M K L P V R L L V L M F W -
 Peptide leader

61 TTTCTGCTTCCAGCAGTGATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACC 120
 -----+-----+-----+-----+-----+
 AAAGGACGAAGGTGTCCTACTACAACACTACTGAGTQAGAGGTGAGAGGGACGGGCAGTGG

2
 F P A S S S D V V M T Q S P L S L P V T -

121 CCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCATTGTACATAGTAATGGA 180
 -----+-----+-----+-----+-----+
 GGACCTCTCGGCCGGAGGTAGAGGACGTCCACATCAGTCTCGTAACATGTATCATTACCT

CDR 1
 P G E P A S I S C R S S Q S I V H S N G -
 KpnI

181 AACACCTATTTGCAATCGTACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCTGATCTAT 240
 -----+-----+-----+-----+-----+
 TTGTGGATAAACGTTACCATGGACGTCTTCGGTCCCGTCAGAGGTGTCGACCACTAGATA

N T Y L Q W Y L Q K P G Q S P O L L I Y -

241 AAAGTTTCTAATCGGCTTTATGGGGTCCCTGACAGGTTGAGTGGCAGTGCATCAGGCACA 300
 -----+-----+-----+-----+-----+
 TTTCAAAGATTAGCCGAAATACCCCGAGGACTGTCCAAGTCACCGTCACCTAGTCCCTGT

CDR 2
 K V S N R L Y G V P D R F S G S Q S G T -

301 GATTTTACACTGAAATCAGCAGAGTGGAGGCTGAGGATGTGGGGTTTATTACTGCTTT 360
 -----+-----+-----+-----+-----+
 CTAAAATCTGACTTTTAGTTCGTCTCACCTCCGACTCCTACAACCCCAAATAATGACGAAA

D F T L K I S R V E A E D V G V Y Y C F -

361 CAAGGTTACATGTTCCGTGGACGTTCCGGCCAAGGGACCAAGGTGGAAATCAAACGTGAG 420
 -----+-----+-----+-----+-----+
 GTTCCAAGTGTAAGGACCTGCAAGCCGGTTCCCTGGTTCCACCTTTAGTTTGCACTC

CDR 3
 O G S H V P W T F G Q G T K V E I K

RamHI

421 TGGATCCTCTGCG 433
 -----+-----
 ACCTAGGAGACGC

FIGURE 20

MluI
 1 CTCAGAACGCGTGCCGCCACCATGAAGTTGCCTGTTAGGCTGTTGGTGCTGATGTTCTGG
 -----+-----+-----+-----+-----+-----+ 60
 CAGTCTTGCGCACGGCGGTGGTACTTCAACGGACAATCCGACAACCACGACTACAAGACC

 M K L P V R L L V L M F W -
 Leader peptide
 61 TTTCTGCTTCCAGCAGTGATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACC
 -----+-----+-----+-----+-----+-----+ 120
 AAAGGACGAAGGTCGTCACTACAACACTACTGAGTCAGAGGTGAGAGGGACGGGCAGTGG
 2
F P A S S S D I V M T Q S P L S L P V T -
 121 CCTGGAGAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCATTGTACATAGTAATGGA
 -----+-----+-----+-----+-----+-----+ 180
 GGACCTCTCCCCCAGGTAGAGGACGTCCAGATCAGTCTCGTAACATGTATCATTACCT
 CDR 1
P G E P A S I S C R S S Q S I V H S N G -
 KpnI
 181 AACACCTATTTGCAATGGTACCTGCAGAAGCCAGGGCAGTCTCCACAGCTCCTGATCTAT
 -----+-----+-----+-----+-----+-----+ 240
 TTGTGGATAAACGTTACCATGGACGTCTTCCGTCCCGTCAGAGGTGTCGAGGACTAGATA

N T Y L C W Y L Q K P G Q S P Q L L I Y -
 241 AAAGTTTCTAATCGGCTTTATGGGGTCCCTGACAGGTTCAAGTGGCAGTGGATCAGGCACA
 -----+-----+-----+-----+-----+-----+ 300
 TTTCAAAGATTAGCCGAAATACCCAGGGACTGTCCAAGTCACCGTCACCTAGTCCGTGT
 CDR 2
K V S N R L Y G V P D R F S G S G S G T -
 301 GATTTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTCCGGTTTATTACTGCTTT
 -----+-----+-----+-----+-----+-----+ 360
 CTAAATGTGACTTTTAGTCGTCTCACCTCCCACTCTACAACCCCAAATAATGACGAAA

D F T L K I S R V E A E D V G V Y Y C E -
 361 CAAGGTTACATGTTCCGTGGACGTTTCGGCCAAGGGACCAAGGTGGAAATCAAACCTGAC
 -----+-----+-----+-----+-----+-----+ 420
 GTTCCAAGTGTACAAGGCACCTGCAAGCCGGTTCCTGGTTCACCTTTAGTTTGCACCTC
 CDR 3
Q G S H V P W T F G Q G T K V E I K
 BamHI
 421 TGGATCCTCTGCG
 -----+-----+-----+-----+-----+-----+ 433
 ACCTACGAGACGC

FIGURE 21

	17	27	CDR 1
7C10 VH	DVQLQESGPGLVKPSQSLTCSVTGYSIT	GGYLWN	WIRQ
AN03' CL	S..Y..
Kabat sgI(A)	E.....S.....T.....D.....	S..WN.

	CDR 2
7C10 VH	FPGNKLEWMG YISYDGTNNYKPSLKD RISITRDTSKNQFFL
AN03' CLN...N...N...N.....
Kabat sgI(A)S.STY.N.....S.....Y..

	84	CDR 3
7C10 VH	KLNSVTNEDTATYYCAR	YGRV-FFDY WGQGTTLTVSS
AN03' CLT.....	E.YGY.....
Kabat sgI(A)	Q.....T.....	G.YGYG.....V.....

FIGURE 22

	Rch 1	30	CDR 1	Rch 2
7C10 VH mouse	DVQLQESGPGLVKPSQSLTCSVTGYSIT	GGYLWN	WIRQ	
human Kabat sgII	Q.....T.....T.S.G.VS	SIWS..	
human VH FUR1'CL	Q.....ET.....T.S.....S	S..Y.S	
human Germline	Q.....ET.....T.S.....S	S..Y.S	

	Rch 2	49	CDR 2	67	71	Rch 3
7C10 VH mouse	FPGNKLEWMG	YISYDGTNNYKPSLKD	RISITRDTSKNQFFL			
human Kabat sgII	P..KG...I.	R.Y.S.STX.N....S	.VT.SV.....S.			
human VH FUR1'CL	P..KG...I.	SMFHS.SSY.N....S	.VT.SV.....S.			
human Germline	P..KG...I.	S.YHS.STY.N....S	.VT.SV.....S.			

	Rch 3	CDR 3	Rch 4
7C10 VH mouse	KLNSVTNEDTATYYCAR	YGRVFFDY	WGQGTTLTVSS
human Kabat sgII	..S...AA...V.....	ELPGGYDVLV.....
human VH FUR1'CL	Q.R...AA...V.....	GRYCSSTSCNWFDPLV.....
human Germline	..S...AA...V.....		

FIGURE 23

		30	CDR 1	48
7C10 VH mouse	DVQLQESGPGGLVKPSQSLTCSVTGYSIT	<u>GGYLWN</u>	WIRQFPGNKLEWMG	
human germline	Q.....ET.....T.S.....	<u>S</u>	S..Y.GP..KG...I.	
VH Humanized 1	Q.....ET.....T.S.....	P..KG.....	
VH Humanized 2	Q.....ET.....T.S.....	P..KG...I.	
VH Humanized 3	Q.....ET.....T.S.....	<u>S</u>P..KG...I.	

	CDR 2	67	71
7C10 VH mouse	<u>YISYDGTNNYKPSLKD</u>	RISITR	DTSKNQFFLKLNSVTNEDTATYYCAR
human germline	S.FHS.SSY.N.....S	<u>VT</u>	<u>SV</u>S...S...AA...V.....
VH Humanized 1	T.S.....	S...S...AA...V.....
VH Humanized 2	<u>VT</u> .S.....	S...S...AA...V.....
VH Humanized 3	<u>VT</u> . <u>SV</u>	S...S...AA...V.....

	CDR 3
7C10 VH mouse	<u>YGRVFFDY</u> WGQGTTLTVSS
human germline	
VH Humanized 1LV.....
VH Humanized 2LV.....
VH Humanized 3LV.....

FIGURE 24

MluI

```

      |
GTCAGAACGCGTGCCGCCACCATGAAAGTGTTGAGTCTGTTGTACCTCTTGACACCCATT
1  -----+-----+-----+-----+-----+ 60
CAGTCTTGCGCACGGCGGTGGTACTTTACAACTCAGACAACATGGAGAACTGTCTGGTAA

      M K V L S L L Y L L T A I -
      Leader peptide
CCTGGTATCCTGTCTCAGGTGCAGCTTCAGGAGTCGGGGCCAGGACTGGTGAAGCCTTCG
61 -----+-----+-----+-----+-----+ 120
GGACCATAGGACAGAGTCCACGTGGAAGTCTCAGCCCGGGTCTGACCACTTCGGAAGC

      P G I L S Q V Q L Q E S G P G L V K P S -
CAGACCCCTGTCCCTCACCTGCACTGTCTCTGGTIACTCCATCACCGCTGCTTATTTATGG
121 -----+-----+-----+-----+-----+ 180
CTCTGGGACAGGGAGTGGACGTGACAGAGACCAATGAGGTAGTGGCCACCAATAAATACC
      30 CDR 1
E T L S L T C T V S G Y S T T G G Y L W -
AACTGGATACGGCAGCCCCCAGGGAGGGACTGGAGTGGATGGGGTATATCAGCTACGAC
181 -----+-----+-----+-----+-----+ 240
TTGACCTATGCCGTGGGGGTCCCTTCCTGACCTCAGCTACCCCATATAGTGGATGCTG
      48
N W I R Q P P G K G L E W M G Y I S Y D -
      KpnI
      |
GGTACCAATAACTACAAACCCTCCCTCAAGGATCGAATCACCATATCAGGTGACACGTCC
241 -----+-----+-----+-----+-----+ 300
CCATGGTTATTGATGTTTGGGAGGCAGTTCCCTAGCTTAGTGGTATAGTGCAGTGTGCAGG
      CDR 2 67 71
G T N N Y K P S L K D R I T I S R D T S -
AAGAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCTGCGGACACTGCAGTGTATTAC
301 -----+-----+-----+-----+-----+ 360
TTCTTGGTCAAGAGGGACTTCGACTCGAGACACTGGCGACGCTGTGACGTCACATAATG

K N Q F S L K L S S V T A A D T A V Y Y -
TGTGCGAGATACGGTAGGGTCTTCTTTGACTACTGGGGCCAGGGAACCCCTGGTCACCGTC
361 -----+-----+-----+-----+-----+ 420
ACACGCTCTATGCCATCCCAGAAGAACTGATGACCCCGGTCCCTTGGGACCACTGGCAG
      CDR 3
C A R Y G R V F F D Y W G Q G T L V T V -

      BamHI
      |
TCCTCAGGTGAGTGCATCCTCTGCG
421 -----+-----+-----+-----+ 445
AGGAGTCCACTCACCTAGGAGACGC

S S -

```

FIGURE 25

MluI
 |
 GTCAGAACGCGTGCCGCCACCATGAAAGTGTGAGTCTGTTGTACCTCTTGACAGCCATT
 -----+-----+-----+-----+-----+ 60
 CAGTCTTGCGCACGGCGGTGGTACTTTCACAACCTCAGACAACATGGAGAACTGTCGGTAA

 M K V L S L L Y L L T A I -
 Leader peptide
 CCTGGTATCCTGTCTCAGGTGCAGCTTCAGGAGTCGGGCCAGGACTGGTGAAGCCTTCG
 -----+-----+-----+-----+-----+ 120
 61 GCAGCATACCACAGAGTCCACGTCGAAGTCTCAGCCCGGGTCTGACCACTTCGGAAGC

 P G I L S Q V Q L Q E S G P G L V K P S -
 GAGACCCTGTCCCTCACCTGCACTGTCTCTGGTTACTCCATCACCGGTGGTTATTTATCG
 -----+-----+-----+-----+-----+ 180
 121 CTCTGGGACAGGAGTGGACGTGACAGAGACCAATGAGCTAGTCGCCACCAATAAATACC
 30 CDR 1
 E T L S L T C T V S G Y S I T G G Y L W -
 AACTCCATACGGCAGCCCCCAGCGAAGGGACTGGAGTGGATCGGCTATATCAGCTACGAC
 -----+-----+-----+-----+-----+ 240
 181 TTGACCTATGCCGTCCGGGGTCCCTTCCTGACCTCAGCTAGCCCATATAGTCGATGCTG
 48
 N W I R Q P P G K G L E W I G Y I S Y D -

 KpnI
 |
 GGTACCAATAACTACAAACCTCCCTCAAGGATCGAGTCACCATATCACGTGACACGTCC
 -----+-----+-----+-----+-----+ 300
 241 CCATGGTTATTGATGTTTGGGAGGGAGTTCTAGCTCAGTGGTATAGTGCACCTGTGCAGG
 CDR 2 67 71
 G T N N Y K P S L K D R V T I S R D T S -
 AAGAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCTGCGGACACTGCAGTGTATTAC
 -----+-----+-----+-----+-----+ 360
 301 TTCTTGGTCAAGAGGGACTTCGACTCGAGACACTGGCGACGCCTGTGACGTACATAATG

 K N Q F S I K I S S V T A A D T A V Y Y -
 TGTGCGAGATACGGTAGGGTCTTCTTTGACTACTGGGGCCAGGGAACCCCTGCTCACCGTC
 -----+-----+-----+-----+-----+ 420
 361 ACACGCTCTATGCCATCCCAGAGAAACTGATGACCCCGGTCCCTTGGGACCAGTGGCAG
 CDR 3
 C A R Y G R V E F D Y W G O G T L V T V -

 BamII
 |
 TCCTCAGGTGAGTGGATCCTCTGCG
 -----+-----+-----+-----+ 445
 421 AGGAGTCCACTCACCTAGGAGACGC

 S S -

FIGURE 26

MluI
 1 CTGAGAACGCGTGCCGCCACCATGAAAGTGTGAGTCTGTGTACCTCTTGACAGCCATT
 -----+-----+-----+-----+-----+ 60
 CAGTCTTGCGCACCGCGGTGGTACTTTCACTCACAACATGGAGAACTGTCGGTAA

 M K V L S L L Y L L T A I -
 Leader peptide
 61 CCTGGTATCCTGTCTCAGGTGCAGCTTCAGGAGTCGGGCCAGGACTGGTGAAGCCTTCG
 -----+-----+-----+-----+-----+ 120
 GGACCATAGGACAGAGTCCACGTGGAAGTCCCTCAGCCCGGGTCTGACCACTTCGGAAGC

 P G I L S Q V Q L O E S G F G L V K P S -
 121 GAGACCCTGTCCCTCACCTGCACTGTCTCTGGTTACTCCATCAGCGGTGGTTATTTATGG
 -----+-----+-----+-----+-----+ 180
 CTCTGGGACAGGGAGTGGACCTGACAGAGACCAATGAGGTAGTCCGCACCAATAAATACC
 30 CDR 1
 E T L S L T C T V S G Y S I S G G Y I W -
 181 AACTGGATACGGCAGCCCCCAGGCAACCGCACTGGAGTGGATCGGGTATATCAGCTACGAC
 -----+-----+-----+-----+-----+ 240
 TTGACCTATGCCGTGCGGGTCCCTTCCTGACCTCACCTACCCCATATAGTCGATGCTG
 48
 N W I R Q P P G K G L E W I G Y I S Y D -
 KpnI
 241 GGTACCAATAACTACAAACCTCCCTCAAGGATCGAGTCACCATATCAGTGGACACGTCC
 -----+-----+-----+-----+-----+ 300
 CCATGGTTATTGATGTTTGGGAGGGAGTTCCTAGCTCAGTGGTATAGTCACCTGTGCAGG
 CDR 2 67 71
 G T N N Y K P S L K D R V T I S V D T S -
 301 AAGAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCTGCGGACACTGCAGTGTATTAC
 -----+-----+-----+-----+-----+ 360
 TTCTTGGTCAAGAGGGACTTCGACTCGAGACACTGGCGACGCCTGTGACGTACATAATG

 K N Q F S L K L S S V T A A D T A V Y Y -
 361 TGTGCGAGATACGGTAGGGTCTTCTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTC
 -----+-----+-----+-----+-----+ 420
 ACACGCTCTATGCCATCCCAGAAGAACTGATGACCCCGGTCCCTTGGGACCACTGGCAG
 CDR 3
 C A R Y G R V F F D Y W G Q G T L V T V -
 BamHI
 421 TCCTCAGGTGAGTGGATCCTCTGCG
 -----+-----+-----+-----+-----+ 445
 AGGAGTCCACTCACCTAGGAGACGC

 S S

FIGURE 27

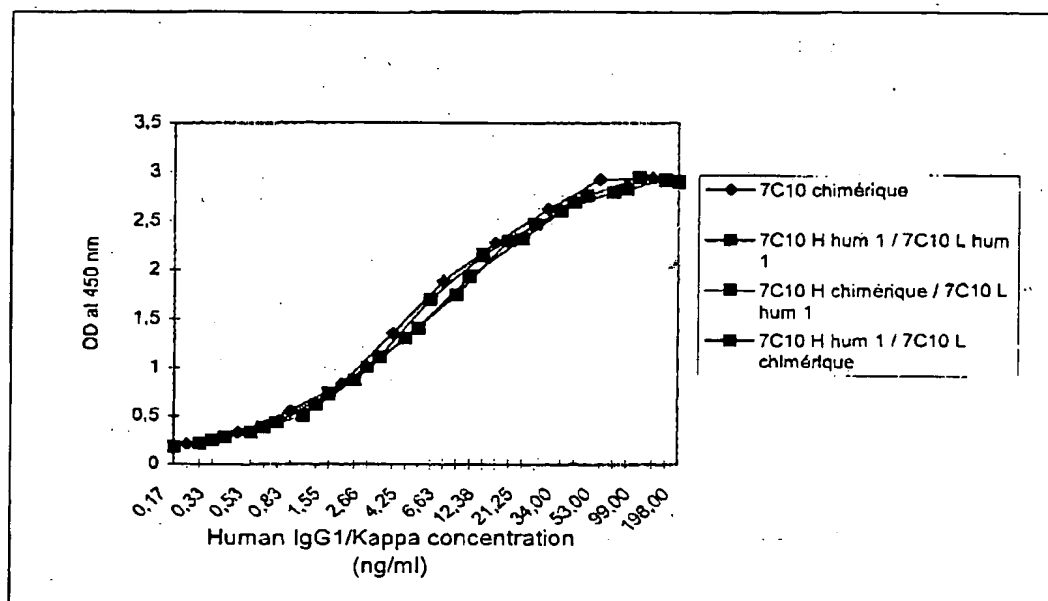


FIGURE 28

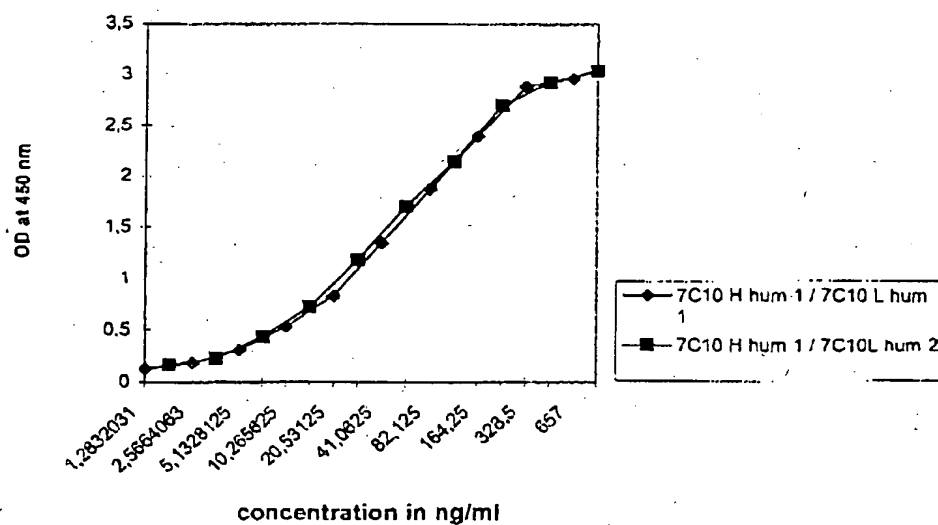


FIGURE 29

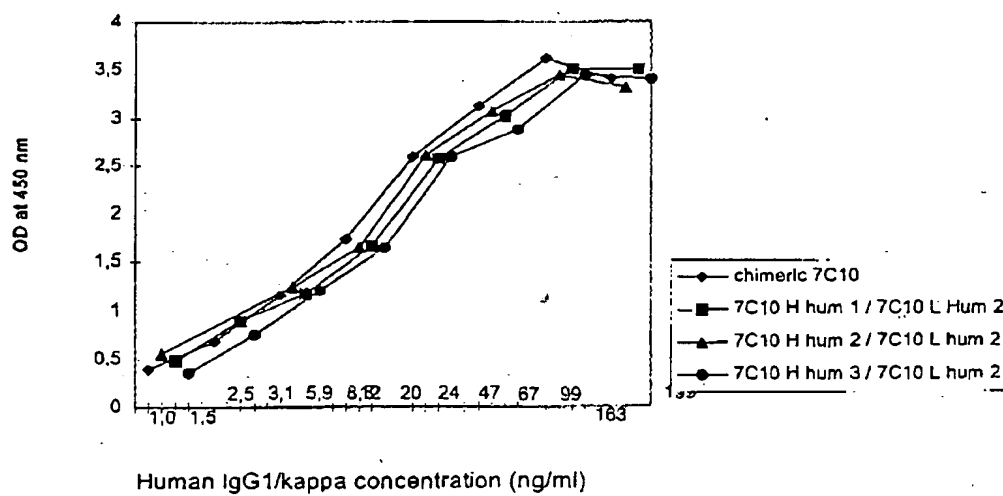
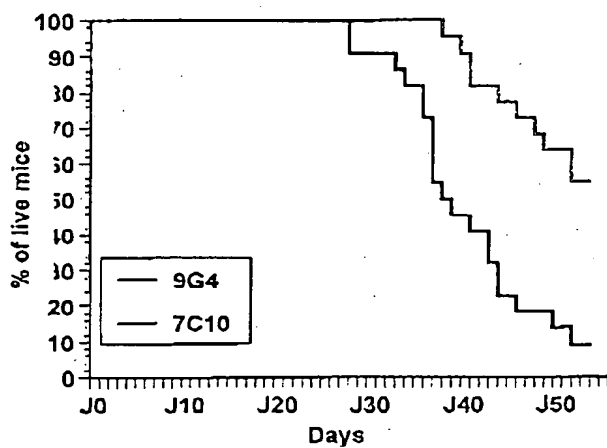


FIGURE 30



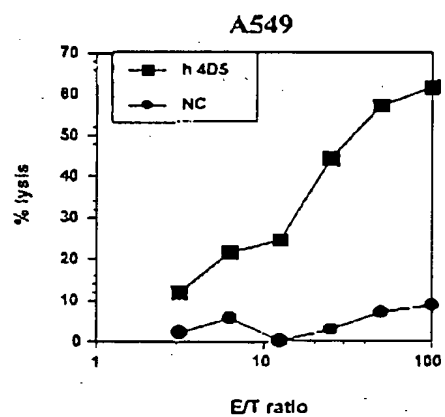


FIGURE 32A

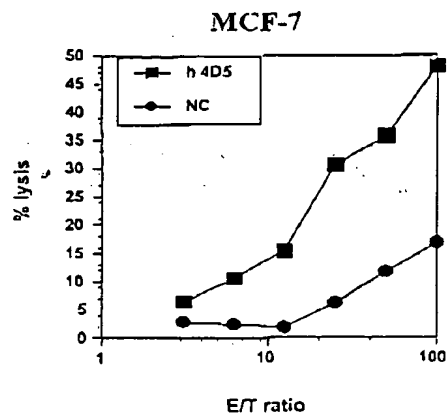


FIGURE 32B

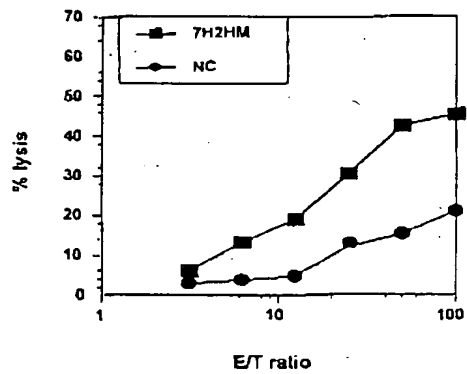


FIGURE 32C

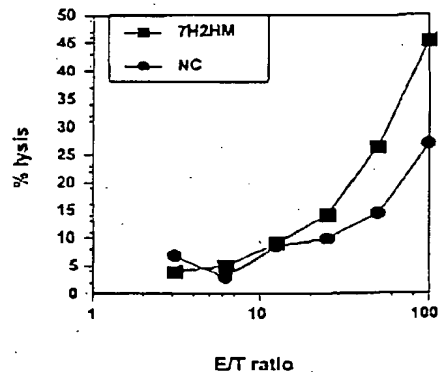


FIGURE 32D

- IGF1

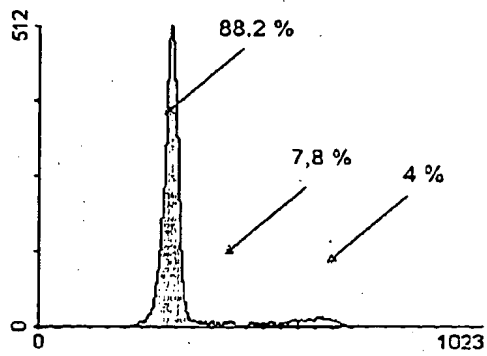


FIGURE 33A

+ IGF1 (50 ng/ml)

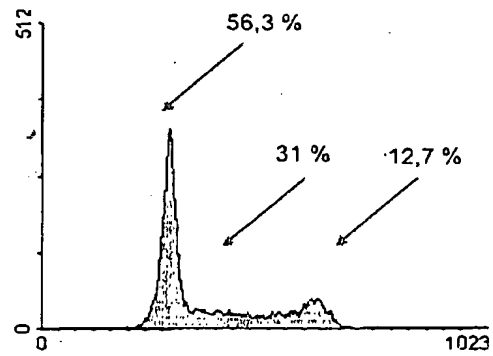


FIGURE 33B

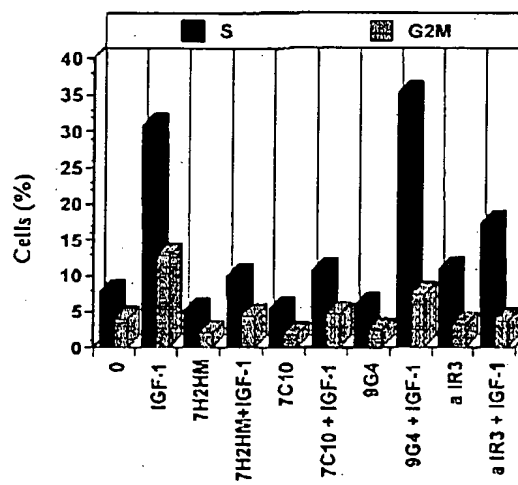


FIGURE 33C

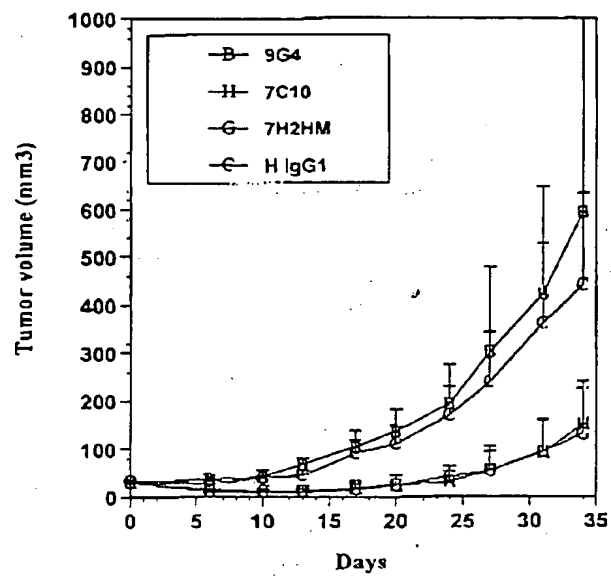


FIGURE 34A

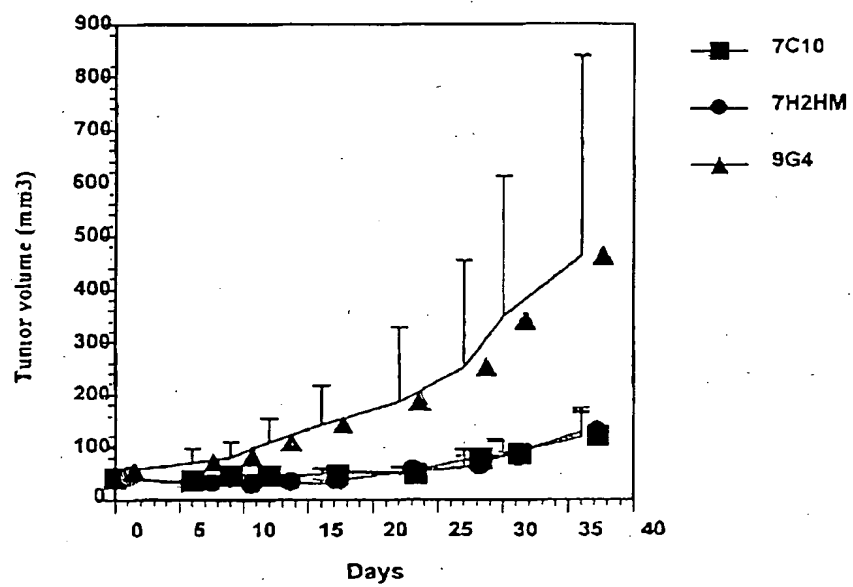


FIGURE 34B

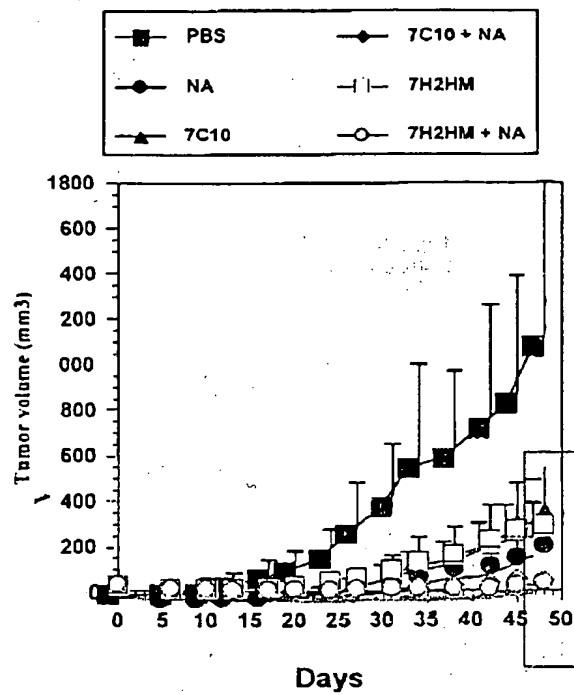


FIGURE 35A

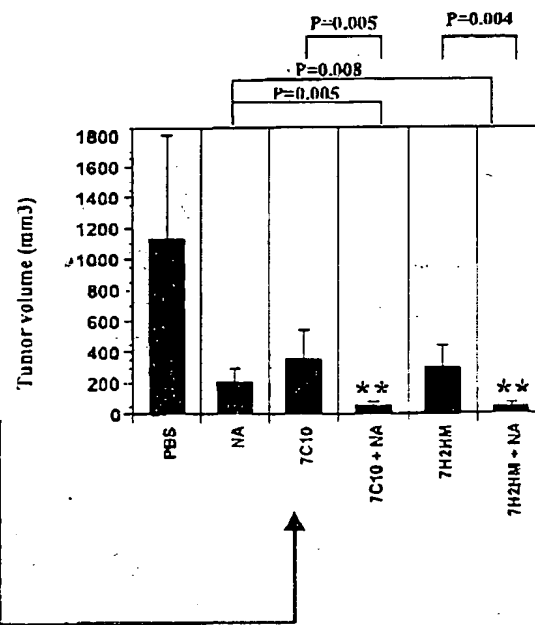


FIGURE 35B

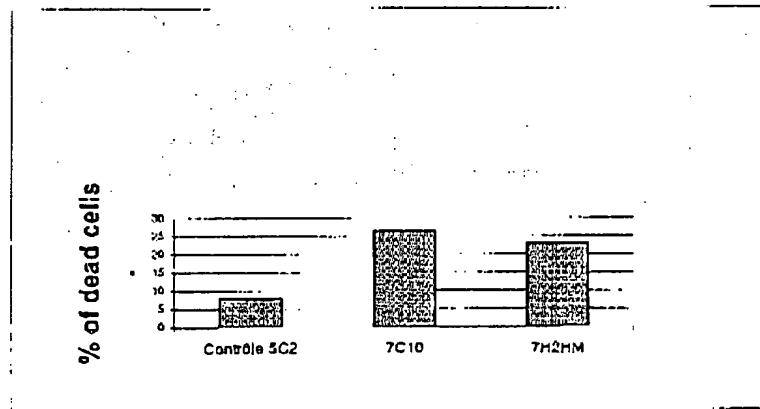


FIGURE 36

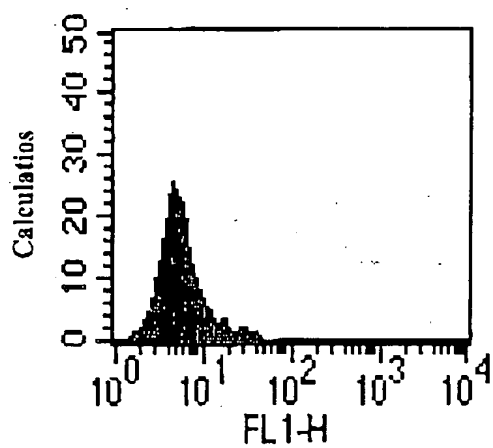


FIGURE 37A

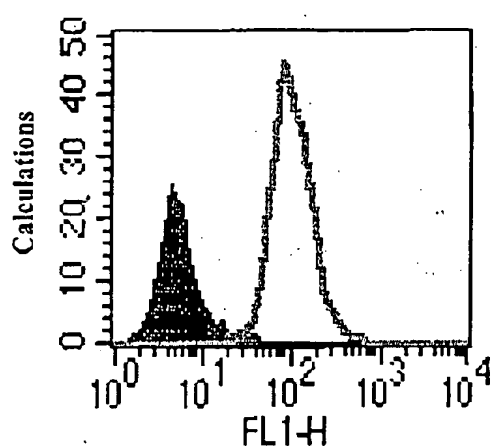


FIGURE 37B

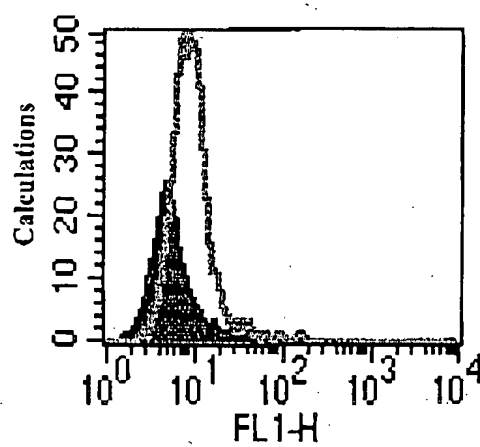


FIGURE 37C

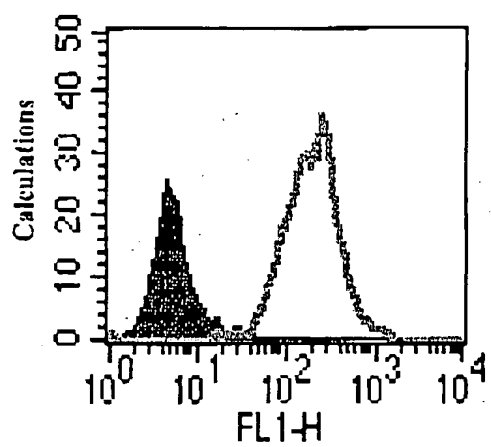


FIGURE 37D

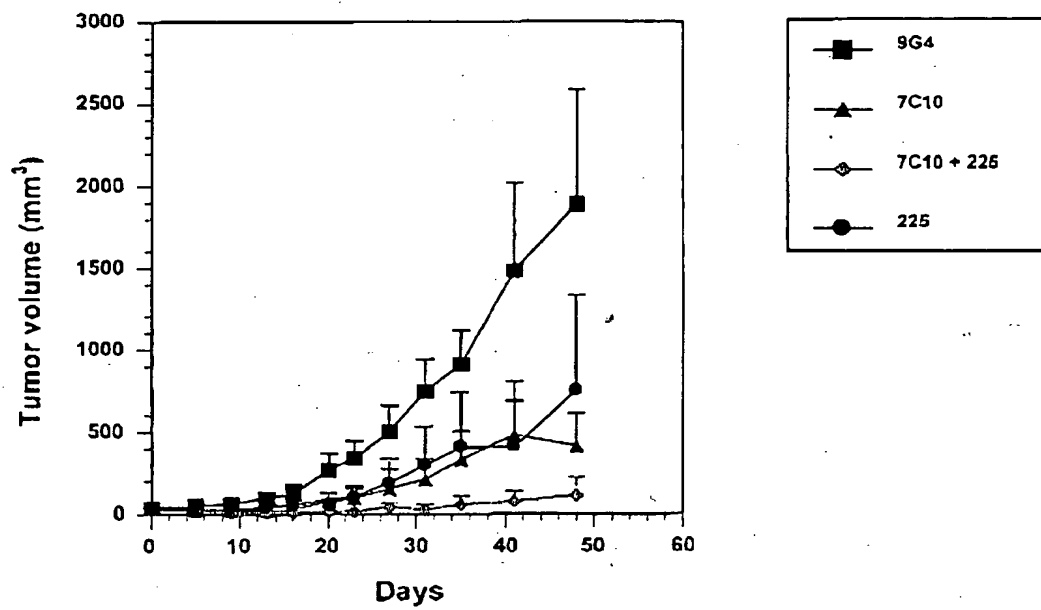


FIGURE 38

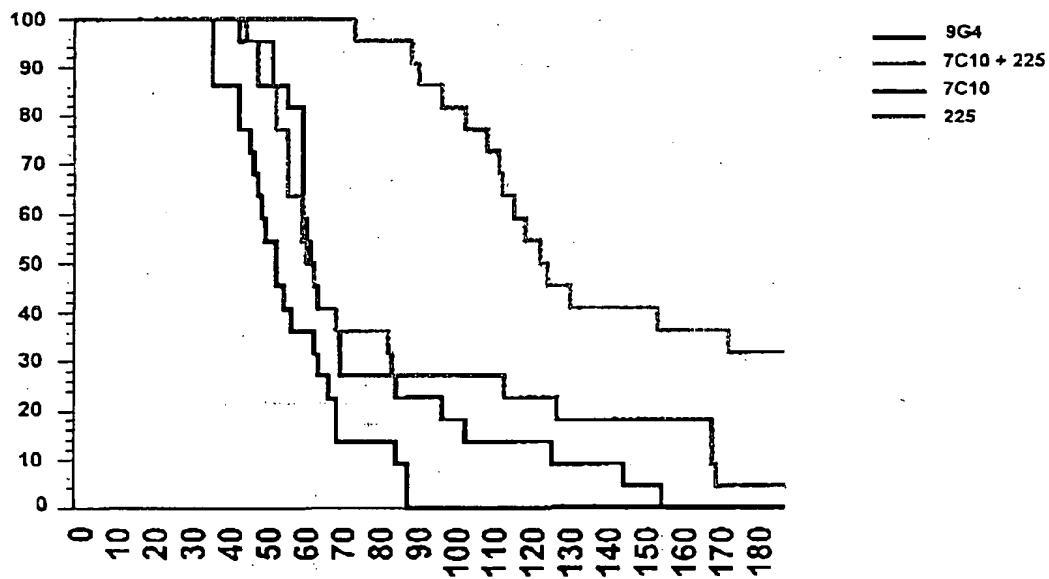


FIGURE 39

FIGURE 40A

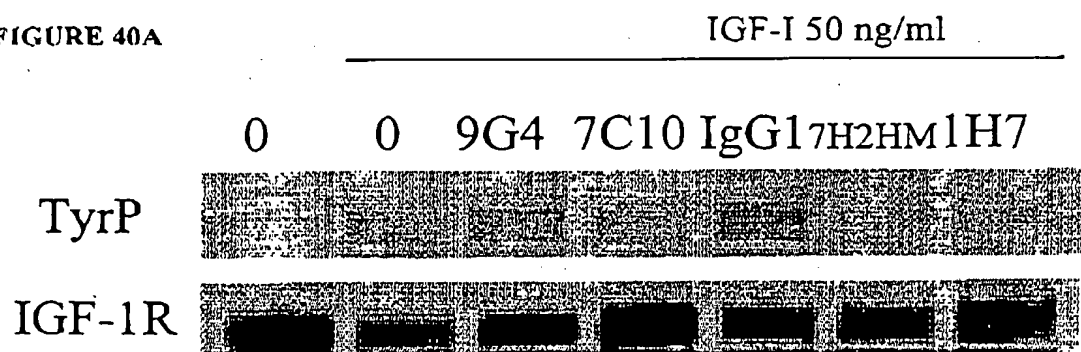


FIGURE 40B

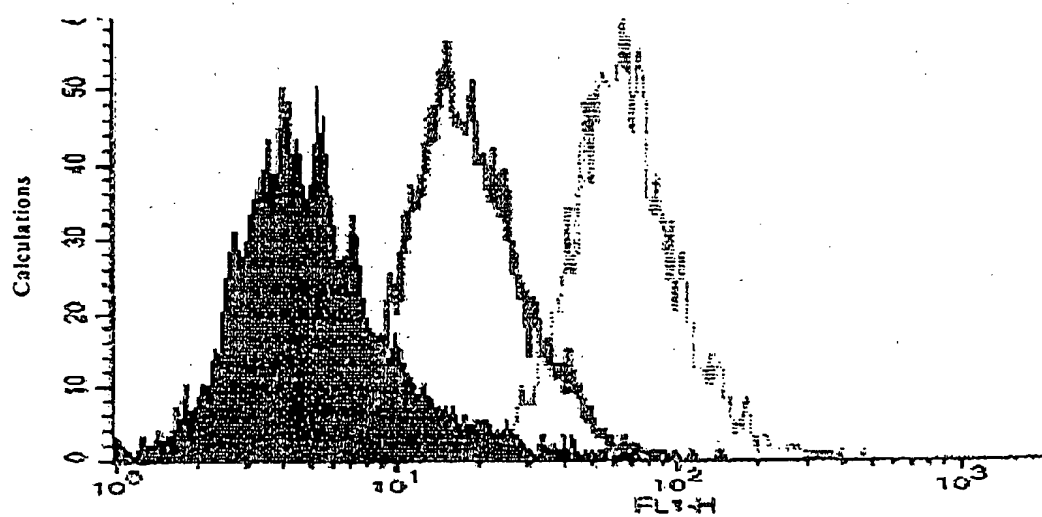
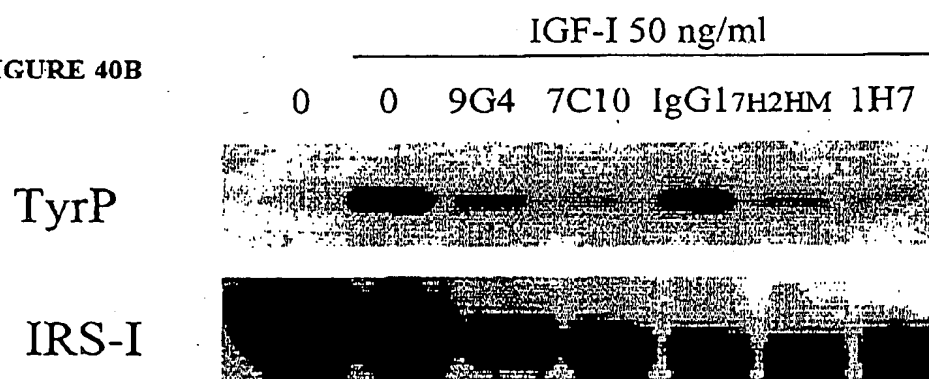


FIGURE 41

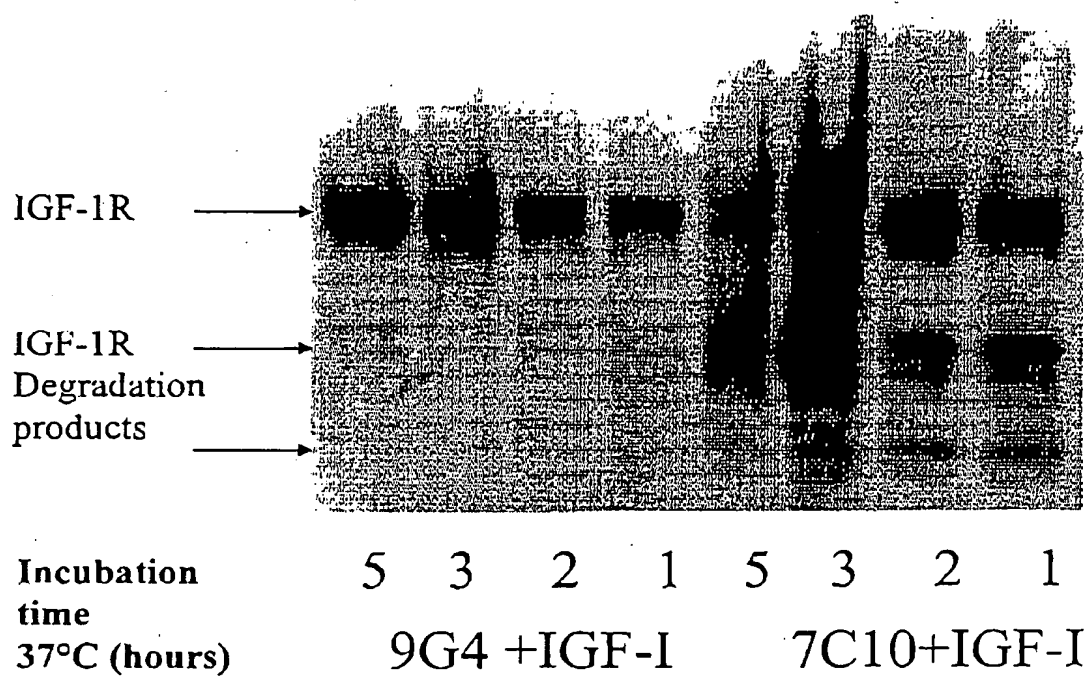


FIGURE 42A

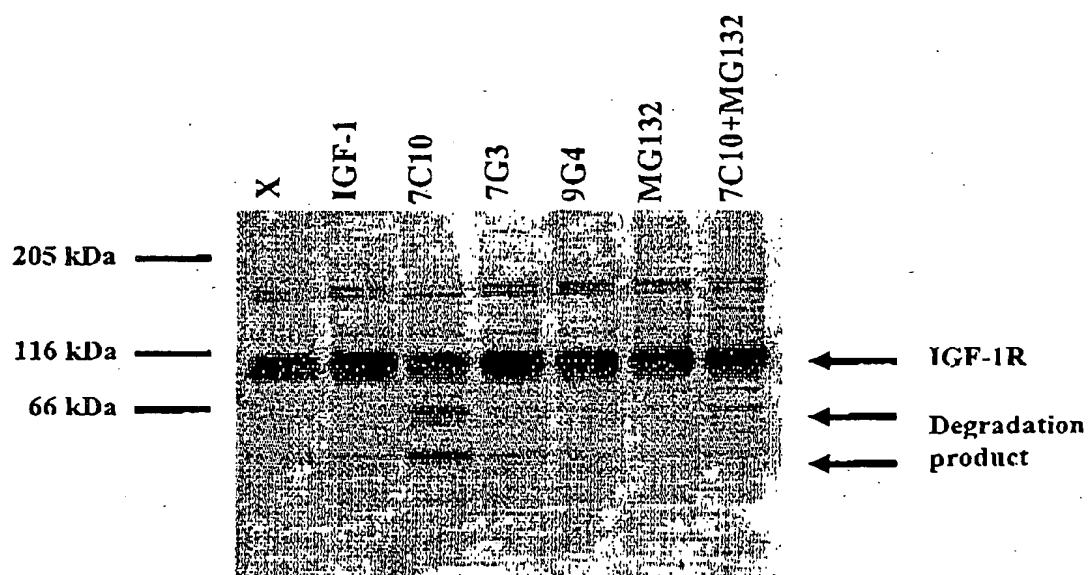


FIGURE 42B

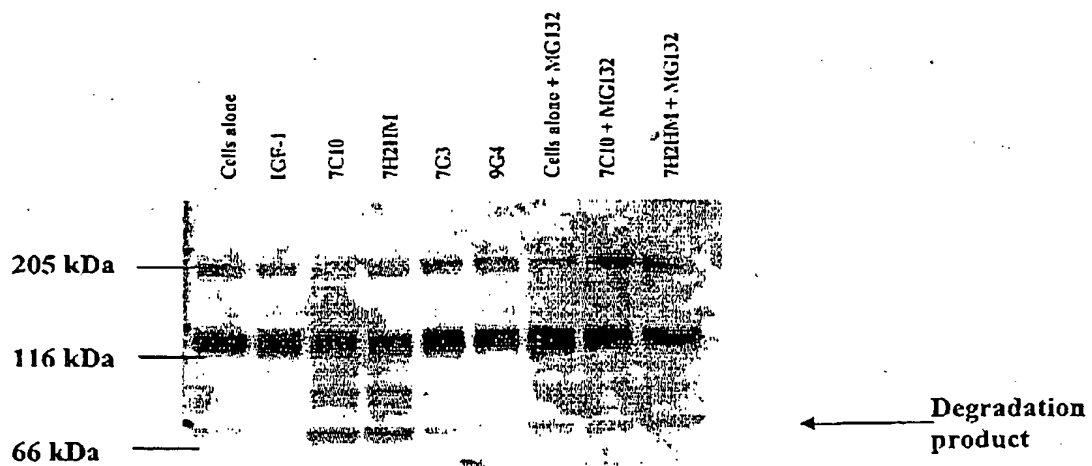


FIGURE 42C

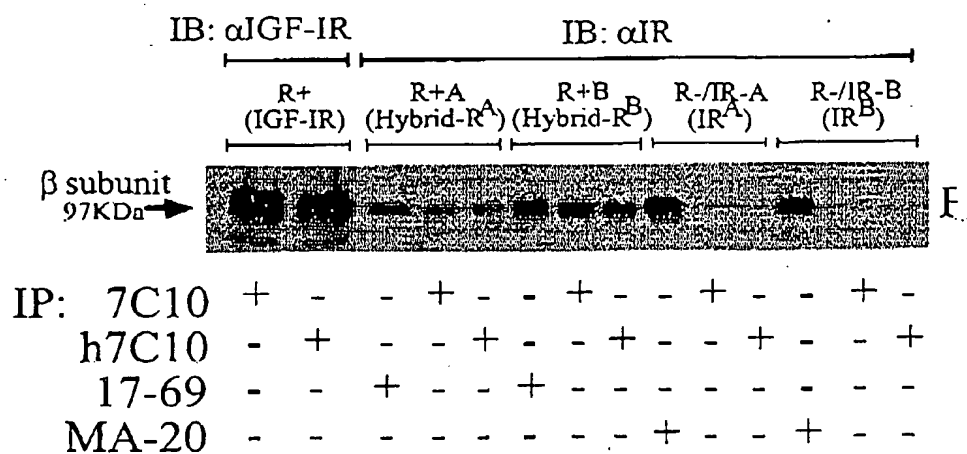


FIGURE 43A

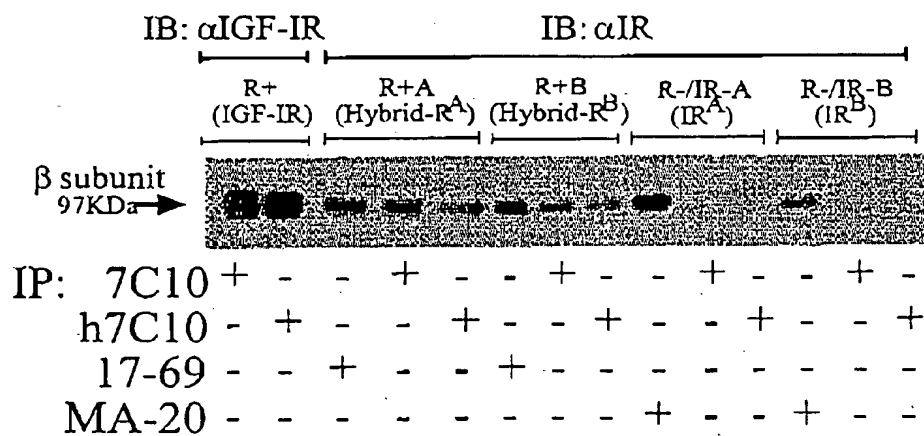


FIGURE 43B

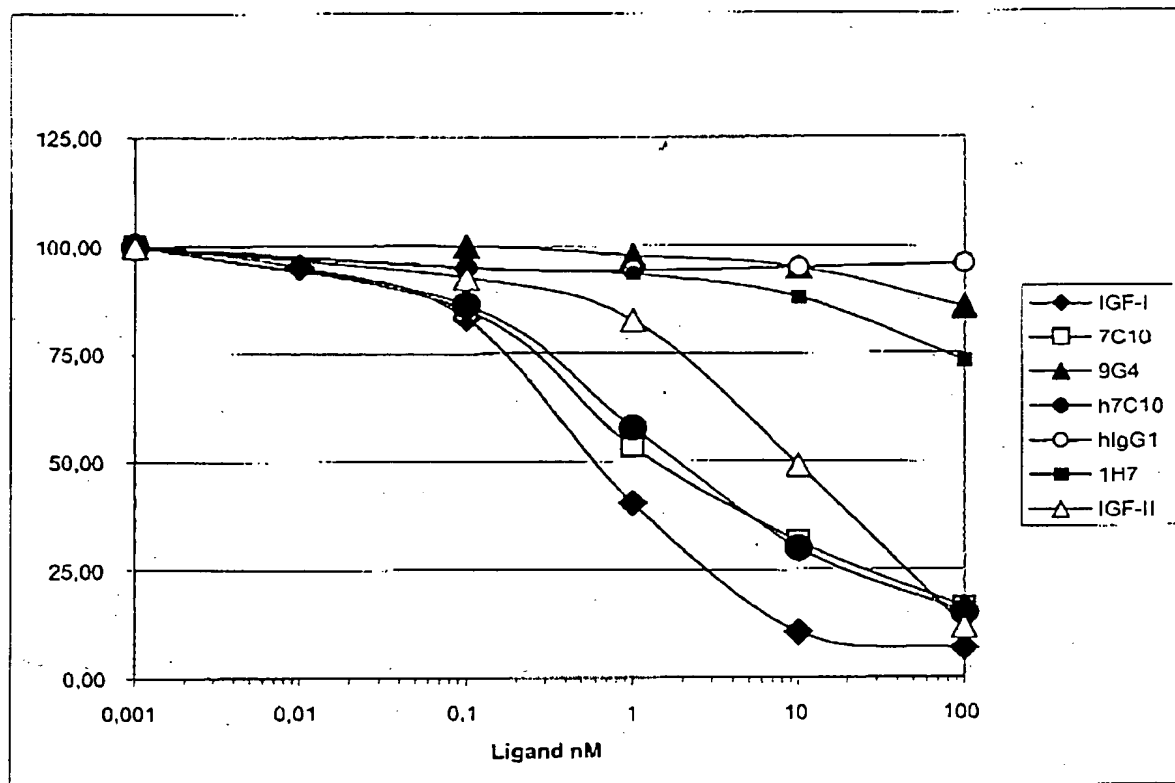


FIGURE 44

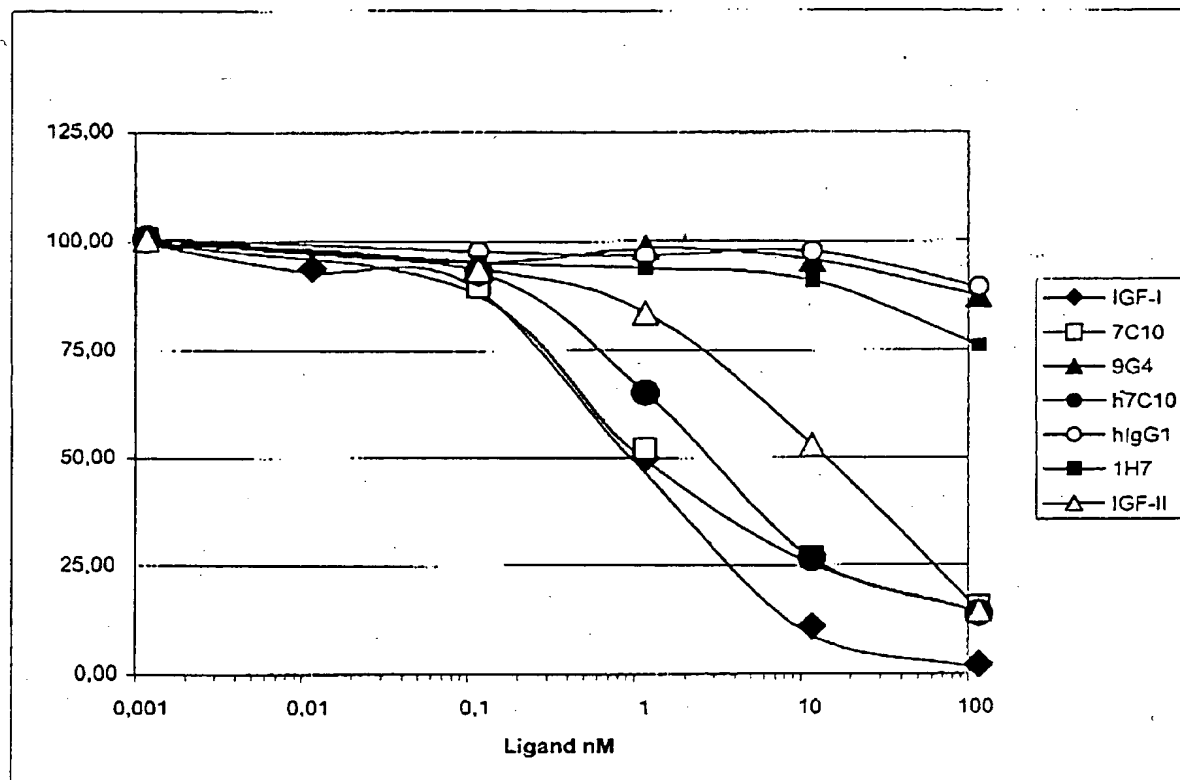


FIGURE 45

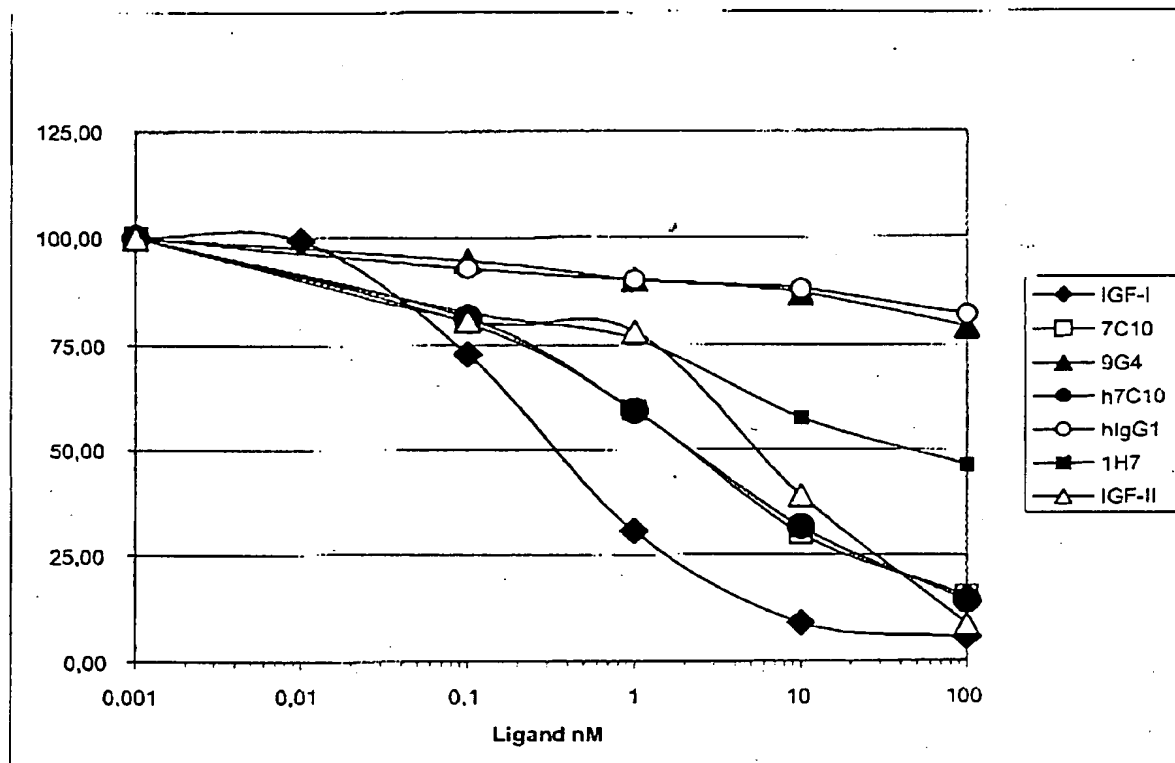


FIGURE 46

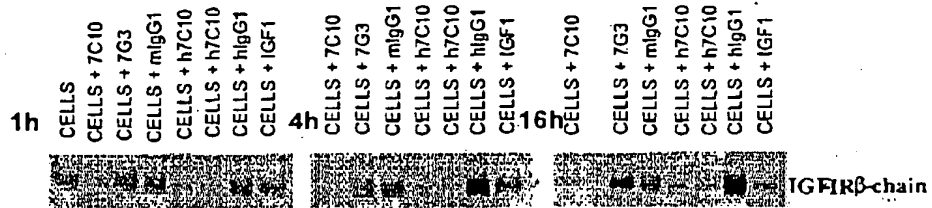


FIGURE 47A

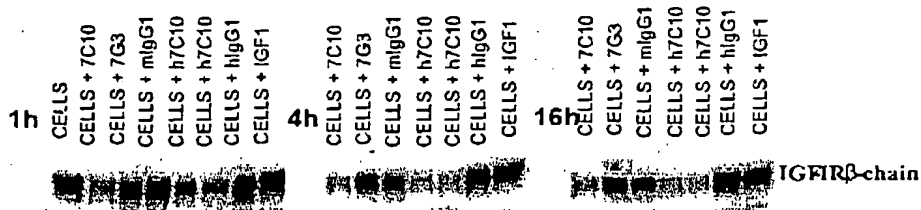


FIGURE 47B

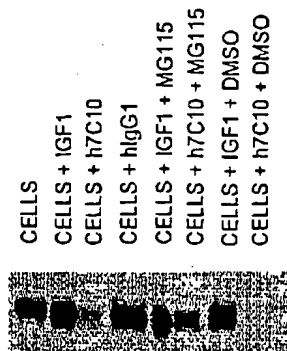


FIGURE 48

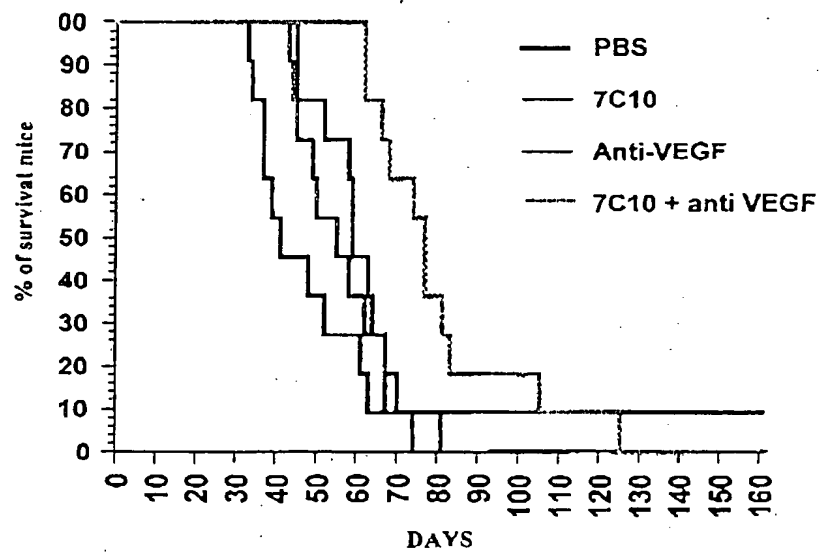


FIGURE 49

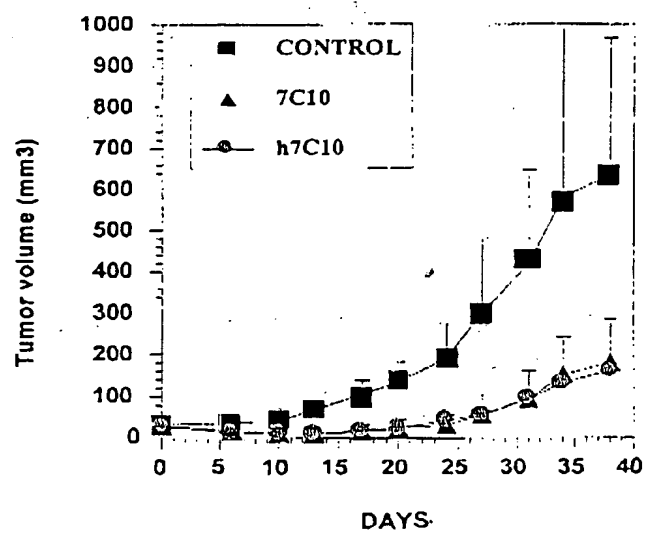


FIGURE 50

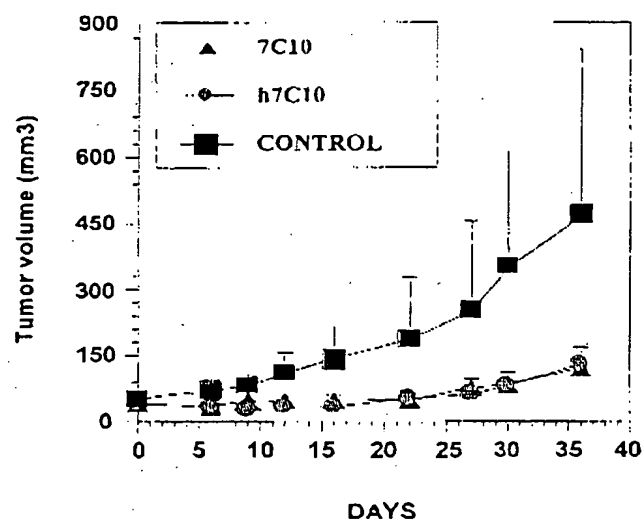


FIGURE 51

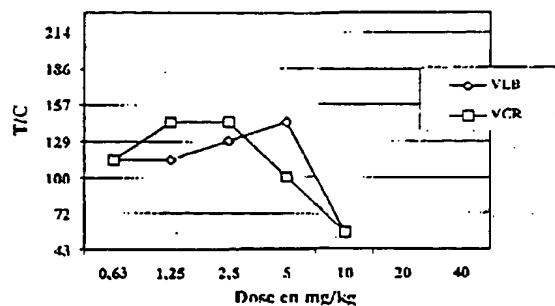


FIGURE 52

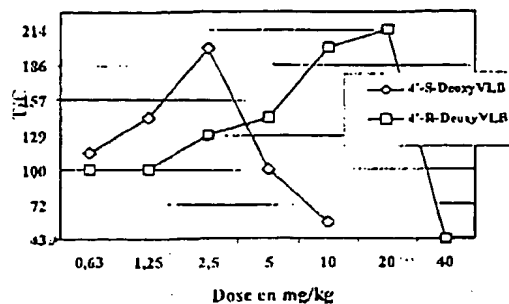


FIGURE 53

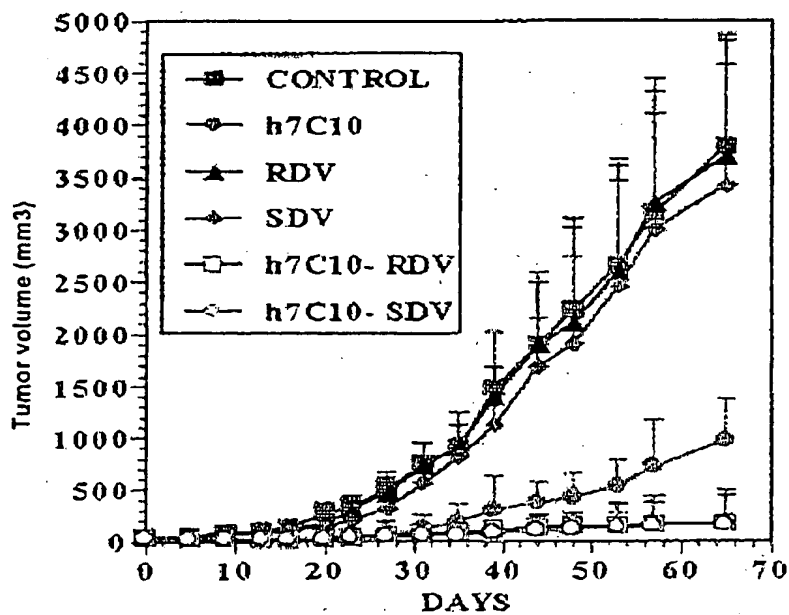


FIGURE 54